UNDERSTANDING AADC DEFICIENCY

Could an underlying rare disorder be the cause of your child's symptoms?

Learn more about Aromatic L-amino Acid Decarboxylase (AADC) deficiency, which can cause symptoms in children, including uncontrolled eye movements (oculogyric crises), low muscle tone (hypotonia), and delays in development.

PTC THERAPEUTICS™

WHAT IS AADC DEFICIENCY?

Aromatic L-amino Acid Decarboxylase (AADC) deficiency is a rare genetic disorder that affects the brain, causes weak muscle tone, and affects how a child develops.

Genetic disorders are caused by an alteration (mutation) in genes.

Genes are found within cells and are made up of DNA. They carry information that determines the traits and characteristics passed down to individuals from their parents. These genes influence how a person looks, including skin, hair, and eye color.

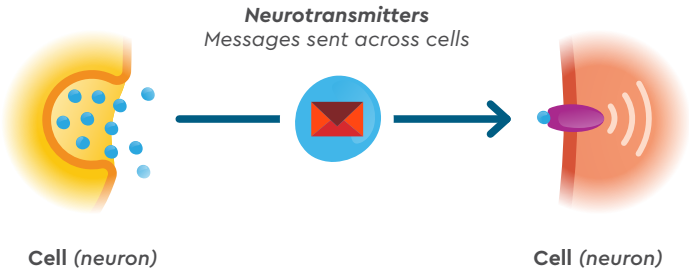
Genes also provide instructions to make building blocks called proteins, such as enzymes. These proteins help to support important functions in the body like digestion, communication between different parts of the body, energy production, and growth.

Sometimes there can be an alteration within a gene, called a genetic mutation. This change can be harmful and lead to genetic health problems or disorders, like AADC deficiency.

WHAT CAUSES AADC DEFICIENCY?

AADC deficiency is caused by an alteration in a gene called the *DDC* (dopa decarboxylase) gene.

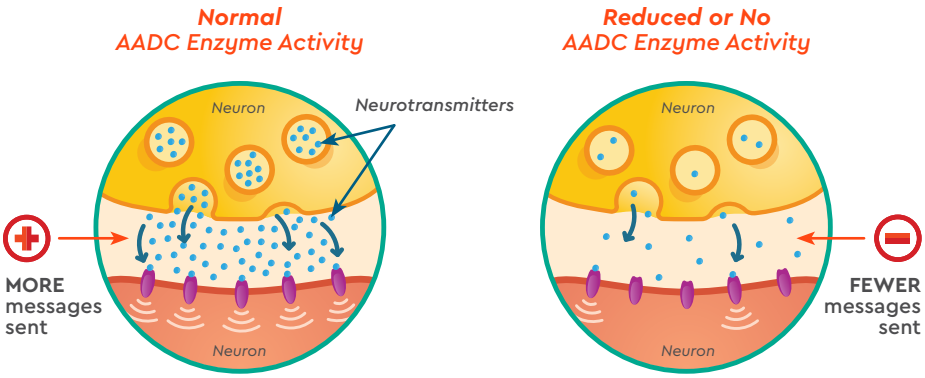
There is a gene in the body called the *DDC* gene that is needed to make an enzyme called AADC. The AADC enzyme helps to make natural chemicals called neurotransmitters.



Neurotransmitters are the messages sent between the cells in the nervous system called neurons. Neurons send and receive messages that are important for controlling different functions in the body, including the senses and motor function. These messages are important because they help to control many of the body's functions.

WHAT HAPPENS IN AADC DEFICIENCY?

AADC deficiency is a disorder that interferes with the way the cells in the nervous system talk to each other.

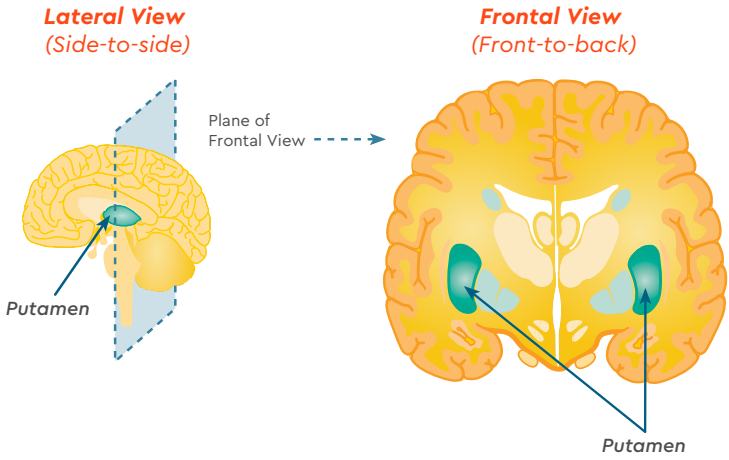


- In AADC deficiency, a change (mutation) within the *DDC* gene leads to a **decrease or no activity of the AADC enzyme**
- This results in a **lower level of neurotransmitters**, like dopamine
- Without enough neurotransmitters (messages), **neurons can't communicate with each other**
- This means the **body can't perform important functions**, which can result in the symptoms of AADC deficiency that limit daily life

Because some neurotransmitter levels are very low in children with AADC deficiency, this condition is considered part of a broader group of genetic disorders called neurotransmitter disorders.

THE ROLE OF THE PUTAMEN IN AADC DEFICIENCY

A major site of dopamine activity is the putamen, a large structure located in the the frontmost region of the brain (forebrain). It is responsible for the planning, execution, and coordination of movement, as well as learning and retaining skills.



Reduced or altered levels of dopamine can reduce communications between neurons, which can result in the loss of motor function.

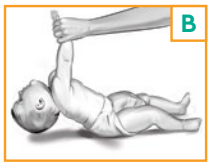
Children with AADC deficiency have lower levels of dopamine, which can reduce the putamen's ability to regulate motor function (i.e., crawling, grasping, holding head upright).

SIGNS AND SYMPTOMS OF AADC DEFICIENCY

The decrease in natural chemicals that send messages in the nervous system (neurotransmitters) that is caused by AADC deficiency may result in a range and severity of symptoms.

The most common symptoms include:

- Low muscle tone, sometimes called "floppy baby" (hypotonia) *(Figures A, B)*



- Delays in development, such as the ability to:
  - Lift and control their head
  - Crawl, sit, or stand without support
  - Babble or say words
  - Walk

Hold head upright
3-4 months

Sitting
6-9 months

Standing
10-12 months

Walking
11-15 months

Milestone	✓	✓	✓	✓
AADC Deficiency	✗	✗	✗	✗

- Increased tightness of muscle tone and reduced ability of the muscle to stretch
- Movement problems, including:
  - Uncontrolled muscle contractions, sometimes called dystonia
  - Uncontrolled eye movements called oculogyric crises *(Figure C)*
    - These uncontrolled upward eye movements can happen suddenly and look like the child is having a seizure by stiffening their muscles and/or twisting *(Figure D)*

People with AADC deficiency may also show signs of:

- Other uncontrolled movements, such as sudden jerking, flailing, or twisting
- Excessive sweating
- Drooling
- Symptoms that become worse or more noticeable later in the day and improve with sleep
- Drooping eyelids
- Stuffy nose

These symptoms may also be present:

- Seizures
- Sleeping problems
- Irritability
- Excessive crying
- Problems with digestion
  - Diarrhea
  - Constipation
  - Reflux
- Problems with feeding

Each individual is different, so not every person will have every symptom, and the severity of symptoms will vary from person to person.

THE CHALLENGE OF A CORRECT DIAGNOSIS

Although symptoms are often seen when the person is still an infant, an accurate diagnosis may take a long time. AADC deficiency is rare and many of its symptoms are similar to other disorders, so it is often misdiagnosed or not diagnosed.

AADC deficiency may be misdiagnosed as the following conditions because they have similar symptoms:

- Epilepsy
- Cerebral palsy
- Mitochondrial disease
- Neuromuscular disorders
- Juvenile parkinsonism*
- Behavioral disorders/autism

The symptoms of dopamine deficiency in juvenile parkinsonism and AADC deficiency may appear similar. However, unlike juvenile parkinsonism, **AADC deficiency involves only a single gene mutation, and its signs and symptoms appear during infancy and do not worsen over time.**

When AADC deficiency is misdiagnosed at first or is never correctly diagnosed, treatment and proper management of this condition is delayed.

*Parkinsonism is a general term that refers to a group of neurological disorders that cause movement problems similar to those seen in Parkinson's disease.

TELLING AADC DEFICIENCY APART FROM OTHER CONDITIONS

These are signs and symptoms that may set AADC deficiency apart from other conditions:

Uncontrolled eye movements called oculogyric crises
Episodes when a child's eyes suddenly roll upward, without control, that can last anywhere from a few seconds to hours, and can happen several times a day or several times a week

Normal or non-distinct brain scans including CT, MRI, and EEG

Multiple symptoms associated with bodily functions such as excessive sweating, droopy eyelids, and a stuffy nose

Symptoms may become worse or more noticeable later in the day and improve with sleep

If your child is showing one or a combination of these signs and symptoms, you may want to talk to your child's doctor about screening for AADC deficiency.

GETTING YOUR CHILD TESTED FOR AADC DEFICIENCY

Get a no-cost genetic test without leaving your home

- If your child has been diagnosed with cerebral palsy (CP) or has signs and symptoms of cerebral palsy without a clear cause, there might be a genetic reason.
- Talk to your child's doctor about getting tested through the **PTC Pinpoint™ Neurotransmitter Disorders program** or the **PTC Pinpoint™ CP Spectrum program**. These are no-cost genetic testing and counseling programs for individuals in the US and Canada who are suspected of having a neurotransmitter disorder or who have symptoms of cerebral palsy (CP) with an unknown cause.
- **PTC Pinpoint Direct™*** is an innovative, sponsored testing program that helps parents get the answers they deserve. It breaks down the barriers to genetic testing for CP by giving parents the ability to directly initiate the testing process, get a sample collection kit sent to their home, and receive expert genetic counseling—all at no cost for eligible patients.

*This program is available for patients with symptoms of CP or patients who have been diagnosed with CP without risk factors for an acquired brain injury. Available in the US only.

Other core tests to diagnose AADC deficiency include:

- **Blood test for AADC enzyme activity:** This test measures the activity of the AADC enzyme, which is lower in patients with AADC deficiency
- **CSF neurotransmitter metabolite panel:** Neurotransmitters allow the cells in the nervous system to talk to each other. This test measures the levels of different compounds (metabolites) involved in the making of neurotransmitters

A positive result from 2 or more of the core tests confirms a diagnosis of AADC deficiency.

Your child's doctor may also order an additional screening test that will be helpful in diagnosing your child:

- **Blood test for 3-OMD**: This simple screening test measures a compound called 3-OMD that can be useful if your child's doctor suspects AADC deficiency

Your child's doctor will work with you to explain what kind of sample is needed for each individual test.

3-OMD=3-O-methyldopa; CSF=cerebrospinal fluid; DDC=dopa decarboxylase.

ASK YOUR CHILD'S DOCTOR IF YOU SUSPECT YOUR CHILD MAY HAVE AADC DEFICIENCY

Aromatic L-amino Acid Decarboxylase (AADC) deficiency is a rare genetic disorder that affects the brain, causes weak muscle tone, and affects how a child develops.

- The most common symptoms of AADC deficiency include low muscle tone, delays in development, and movement disorders, such as oculogyric crises
- Genetic testing options are available to confirm a diagnosis of AADC deficiency, including PTC Pinpoint Direct™, a no-cost program for individuals in the US or Canada suspected of having a neurotransmitter disorder, such as AADC deficiency
  - With PTC Pinpoint Direct you can initiate a no-cost genetic testing for your child and have a sample collection kit sent directly to your home

Ask your child's doctor for more information about this disorder and testing if you suspect your child has AADC deficiency.

Please visit AboutAADC.com for more information.

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